Complete Summary

GUIDELINE TITLE

Viral hepatitis.

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Viral hepatitis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2008 Mar 10 [Various]. [2 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Viral hepatitis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2005 Oct 7 [Various].

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Viral hepatitis, including:

- Hepatitis A virus (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Delta agent (Hepatitis D) (HDV)
- Hepatitis E virus (HEV)
- Other forms of viral hepatitis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Infectious Diseases
Internal Medicine
Pediatrics
Preventive Medicine

INTENDED USERS

Health Care Providers
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.

TARGET POPULATION

Patients at risk for or with known viral hepatitis

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Evaluation of clinical picture
2. Laboratory tests
3. Liver biopsy (chronic hepatitis)

Prevention

General

1. Food and water hygiene
2. Precautions in risk occupations and sexual relationships

Hepatitis A

1. Avoidance of susceptible foods in high-risk countries
2. Gamma globulin
3. Vaccination

Hepatitis B

1. Avoidance of high-risk behavior and blood contact
2. Vaccination of risk groups
3. Post-exposure prophylaxis with anti-hepatitis B immunoglobulin
4. Cleaning wound after exposure to infectious blood

Hepatitis C

Avoidance of intravenous drug use, tattooing, unprotected sexual intercourse

Treatment/Management

Hepatitis A

1. Weekly monitoring of serum ALT concentrations
2. Hospital referral, as necessary

Hepatitis B

1. Determine hepatitis B surface antigen (HBsAg) and hepatitis B core antibodies from suspected source and exposed person
2. Hepatitis B immunoglobulin and vaccine
3. Weekly monitoring of serum ALT concentrations, prothrombin time, prealbumin and albumin

Acute Hepatitis

1. Antihistamines or cholestyramine for pruritus
2. Assessment of serum albumin and prothrombin time
3. Avoidance of all drugs metabolized in the liver
4. Diet with plenty of calories and carbohydrates

Acute Fulminant Hepatitis (A, B, or C)

1. Intensive care
2. Liver transplantation

Chronic Hepatitis B

1. Interferon alpha
2. Oral lamivudine, telbivudine or adefovir

Chronic Hepatitis C

1. Interferon-alpha

2. Pegylated interferon and ribavirin
3. Liver biopsy
4. Monitoring by HCV-polymerase chain reaction (PCR) testing
5. Liver transplantation

MAJOR OUTCOMES CONSIDERED

- Efficacy of prophylaxis
- Efficacy of treatment
- Adverse events related to prophylaxis/treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The evidence reviewed was collected from the Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). In addition, the Cochrane Library and medical journals were searched specifically for original publications.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classification of the Quality of Evidence

Code	Quality of Evidence	Definition
A	**High**	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial

Code	Quality of Evidence	Definition
B	**Moderate**	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	**Low**	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	**Very Low**	Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence • One or more studies with very severe limitations

GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 (modified by the EBM Guidelines Editorial Team).

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence [A-D] supporting the recommendations are defined at the end of the "Major Recommendations" field.

Basic Rules

- Hepatitis A and E can be best prevented by adequate food and drinking water hygiene, particularly in high-risk countries.
- Hepatitis B and C can be prevented by exercising due care in high risk occupations and in sexual behaviour. The single most important risk factor for hepatitis C is intravenous (IV) drug abuse.
- Prophylaxis against hepatitis A by vaccination is indicated before travelling to high-risk countries.
- Hepatitis B vaccination is indicated in high-risk occupations (Chen & Gluud, 2005) [**B**] and for risk groups.
- **Note**: Vaccination recommendations in this article are based on Finnish guidelines.

Basic Rules of Diagnosis

- If acute viral hepatitis is suspected, the following tests should be performed: immunoglobulin M (IgM) antibodies to hepatitis A virus (anti-HAV IgM), hepatitis B surface antigen (HBsAg), IgM antibodies to hepatitis B core antigen (anti-HBc IgM), and hepatitis C virus (HCV) antibody test.
- If clinically mild hepatitis is associated with symptoms suggestive of mononucleosis (fever, lymphadenopathy, splenomegaly, upper respiratory symptoms) the following additional tests are indicated: mononucleosis rapid test or Epstein-Barr virus (EBV) antibody test and cytomegalovirus (CMV) antibody test.

Hepatitis A

Incubation Period

- 15 to 50 days

Route of Infection

- Usually faecal-oral route

Clinical Picture

- Acute onset
- Loss of appetite and nausea are the initial symptoms
- Fever
- Jaundice

Laboratory Tests

- Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are increased.
- A specific diagnosis can be made by determining serum anti-HAV IgM.
- Total antibodies can be determined to assess the need for prophylaxis. A positive test for total antibodies (and a negative result for IgM antibodies) is indicative of an earlier infection that protects against the disease.
- See Figure 1 in the original guideline document.

Prophylaxis

- Avoidance of susceptible foods (especially mussels and other seafood) when travelling in high-risk countries
- Short-term, 80% protection may be provided by an injection of gamma globulin (suitable for short journeys lasting less than 1 or 2 months. The dose is 2 mL intramuscularly (i.m.) for adults and 0.02 to 0.04 mL/kg for children.
- Those who stay a long time in, or travel frequently to, high-risk countries should be vaccinated.
    - For children aged 15 or over and for adults, two doses (Havrix® 1440 ELISA-U/mL, 1 mL) of vaccine are given at months 0 and 6 to 12.
    - For children aged 1 to 15 years, half the adult dose (0.5 mL) is given similarly in two doses at months 0 and 6 to 12.
    - The dose of Epaxal® vaccine is given the same for adults and children over 2 years of age.
- Hepatitis A+B combination vaccine
    - Given in three doses at months 0, 1, and 6
    - A separate vaccine is available for children below 16 years of age.
- Hepatitis A prophylaxis is always recommended for tourists travelling to the tropics and to the African and Middle Eastern coasts of the Mediterranean. For the Baltic countries, Russia, and former Eastern European countries, prophylaxis is recommended if the intended stay is of a long duration or repeated visits are anticipated.

Contagiousness

- One week after the onset of jaundice the virus is no longer excreted in the faeces.
- No permanent carrier status has been identified.

Course of the Disease and Follow-up

- The disease is self-limiting, and no specific treatment is available.
- Serum ALT concentrations should be monitored weekly until they start to decline.

Hepatitis B

Incubation Period

- 1 to 6 months

Route of Infection

- Parenteral (syringes used in IV drug use, blood products)
- Sexual contact
- Perinatal transmission

Clinical Picture

- Similar to that in hepatitis A, but the onset is often slower
- Joint symptoms in 10% to 20% of patients
- Skin symptoms
- Liver transaminase concentrations rise more slowly than in hepatitis A

Laboratory Diagnosis

- Increased serum ALT and AST.
- A specific diagnosis is made by determining serum HBsAg and anti-HBc IgM.
- For assessment of infectiousness, the presence of hepatitis B e-antigen (HBeAg) should be determined. (If the result is positive, the patient is likely to have active hepatitis and the disease is much more infectious as the virus is actively replicating.)
- See Table 1 and Figure 2 in the original guideline document.

Prophylaxis

- Avoidance of high-risk behaviour (unprotected sex with potential virus carriers, use of unclean injection needles)
- Avoidance of blood contact in occupations that involve contact with human blood

Vaccination of Risk Groups

- Target groups
    - Neonates with parents who are HBsAg positive (Lee et al, 2006; Andre & Zuckerman, 1994) [**A**]. If the mother is a carrier the child should also be given, before the first vaccination, a dose of anti-hepatitis B immunoglobulin (125 IU).
    - Persons living with HBsAg carriers or with patients with an acute hepatitis B infection
    - Sexual partners of HBsAg carriers and sexual partners of patients with an acute hepatitis B infection
    - People with a bleeding disorder requiring regular treatment with blood products

    - IV drug abusers, their regular sexual partners, and others living in the same household. It is particularly important to vaccinate newborn babies of mothers who use illicit IV drugs.
    - Persons involved in prostitution
    - After needle stick injuries and blood exposure when, according to a risk assessment, prophylaxis is required and the case cannot be referred to the occupational health care.
    - Health workers planning to work in endemic areas
- Vaccination against hepatitis B may also be considered in individual cases for persons who, due to their work (Chen & Gluud, 2005) [**B**], are at an increased risk of blood contact. Vaccination may also be considered for those under the care of such a person. For example:
    - Midwives, dental surgeons, and certain laboratory personnel
    - Staff working at a dialysis unit treating a patient who is a HBsAg carrier. Other patients of such a unit
    - Staff at a child care centre caring for a child who is an HBsAg carrier. Other children of such a centre
    - Anyone involved in the care of IV drug abusers
- Administration of the vaccine
    - Hepatitis B vaccine 1.0 mL i.m. (0.5 mL for children)
    - The dose is repeated at 1 and 6 months. No booster injections are usually necessary after a successful initial vaccination.
    - About 10% of the vaccinated persons do not obtain sufficient immunity. If the risk of exposure to the virus is high and long-lasting, the presence of immunity should be confirmed serologically about 2 months after the third injection (Chen & Gluud, 2005) [**B**]. If there is no antibody response, three additional doses are given at intervals of two months and the presence of immunity is confirmed serologically about two months after the third injection. If there is still no antibody response, the risk of exposure should be decreased by, for example, job re-arrangements.

Immune Prophylaxis After Exposure to the Virus

- Hepatitis B immunoglobulin (HepBQuin®) should be given to neonates of HBsAg positive mothers (+ HBV vaccinations) (Lee et al., 2006; Andre & Zuckerman, 1994) [**A**].

Action After Exposure to Infectious Blood

- For detailed instructions, see the Finnish Medical Society Duodecim guideline "Occupational Exposure to Viral Agents."

Contagiousness

- Most patients with hepatitis B infection recover; however, a small proportion (<5%) of adult patients remain carriers of the virus (in the Nordic countries).
- The determination of HBeAg is helpful in the assessment of infectivity in HbsAg positive patients.

Course of the Acute Disease and Follow-up

- Most cases are self-limiting.
- In the active stage of the disease serum ALT, prothrombin time and, if necessary, prealbumin and bilirubin concentrations are monitored weekly until they start to return to normal.
- HBsAg should be determined 3 months after disease onset.

Chronic Stage of the Disease

- If the HBs Ag test remains positive 6 months after the disease onset, the patient is likely to have become a hepatitis B carrier. The carrier status is confirmed by a positive HBsAg test at 12 months.
- The risk of hepatoma is increased in chronic carriers of hepatitis B.

Hepatitis C

- The most common type of hepatitis in most countries.
- Most cases of non-A-non-B hepatitis after transfusion have been caused by hepatitis C. There are about 500 million carriers of hepatitis C.

Incubation Period

- 20 to 120 days

Route of Infection

- Parenteral as in hepatitis B but the infectivity is much lower. Sources of exposure include IV drug abuse, tattooing, blood transfusion, and unprotected sex with a hepatitis C positive partner. However, the chance of contracting the virus through unprotected sex is fairly low, and safe sex is not considered absolutely necessary in long-term relationships.
- Hepatitis C was a common cause of transfusion hepatitis before the introduction of screening of blood products for hepatitis C virus.
- There are patients who contract hepatitis C without having ever received blood transfusions or belonging to any of the risk groups.

Clinical Picture

- The clinical presentation is usually mild. Only about 25% of infected individuals develop jaundice, compared with 50% of those infected with hepatitis B. Some patients remain asymptomatic.
- Extrahepatic manifestations such as essential cryoglobulinaemia, glomerulonephritis, autoimmune thyroiditis, Sjögren's syndrome, and porphyria cutanea tarda have been reported in patients with chronic hepatitis C.

Laboratory Diagnosis

- Fluctuating hepatic transaminase (ALT) concentrations are often the only manifestation of hepatitis C. The concentrations may periodically return to normal.
- Serum ALT and AST concentrations rarely exceed 800 U/L.

- A specific diagnosis is obtained by determining antibodies against hepatitis C and by RNA (HCV-RNA).
    - Antibodies can be detected 10 weeks after exposure.
    - HCV RNA is usually positive from at symptom onset.

Contagiousness

- The majority of patients with antibodies are also carriers of the virus and may spread the infection.

Course of the Disease and Follow-up

- Alcohol predisposes the patient to complications of hepatitis C.
- The acute phase is often milder than in hepatitis B but the disease becomes chronic more often (in 50% to 80% of patients).
- Transaminase assays are not helpful in the acute phase because they tend to fluctuate. Monitoring is, however, important if specialist consultation is anticipated.
- The average times from primary infection to liver disease are: chronic hepatitis 13 years, active hepatitis 18 years, cirrhosis 21 years, and hepatoma 28 years. Some patients (20% to 30%) develop cirrhosis of the liver as soon as 5 to 7.5 years after contracting the disease.

Delta Agent (Hepatitis D)

- Occurs as a superinfection with hepatitis B.
- Caused by a satellite virus that can only infect a HBsAg positive person (both viruses can be acquired at the same exposure).
- Usually IV drug abusers and in HBV carriers.
- The course of the disease can be fulminant.
- A specific diagnosis can be made by determining serum antibodies against hepatitis D virus (HDV) and, if needed, by demonstration of HDV-RNA.
- Treatment with interferon alpha has been tried (Malaguarnera et al., "A meta-analysis," 1996) [**B**].

Hepatitis E

- A disease resembling hepatitis A that occurs mainly in developing countries.
- A specific diagnosis can be made by determining serum IgG and IgM antibodies to hepatitis E virus (anti-HEV IgG and anti-HEV IgM).
- Hepatitis E should be suspected in patients who have recently visited a developing country, and are likely to have contracted the disease by an oral route, but who have no antibodies against hepatitis A.
- During pregnancy hepatitis E may be particularly fulminant with resultant maternal mortality up to 20%.
- Treatment and follow-up are carried out as in hepatitis A.

Other Forms of Viral Hepatitis

- Some cases of hepatitis remain without an aetiological diagnosis. It is therefore possible that hepatitis viruses other than those described above do exist.
- Up to 90% of patients with mononucleosis induced by Epstein-Barr or cytomegalovirus develop hepatitis. The disease is usually mild, and only about 5% of the patients develop jaundice.

Treatment of Hepatitis and Indications for Specialist Intervention

Acute Hepatitis

- The severity is assessed by determining serum albumin and prothrombin time. The disease is mild if prothrombin time is over 40% and serum albumin above 30g/L.
- Pruritus can be treated by antihistamines or cholestyramine (4 g/day).
- All drugs that are metabolized in the liver should be avoided.
- The diet should contain plenty of calories and carbohydrates.

Acute Fulminant Hepatitis (A, B or C)

- Deep jaundice, cerebral symptoms, progressing liver damage.
- Intensive care is indicated. Liver transplantation may be life-saving.
- Antiviral medication is not helpful in the acute phase.

Chronic Hepatitis B

- With interferon-alpha therapy (4 to 6 months), HBeAg disappears from serum in 35% of the patients (Malaguarnera et al., "The effiacy of interferon-alpha," 1996) [**A**]. Instead of interferon, oral lamivudine, telbivudine or adefovir may be used. In users of intravenous drugs, abstinence lasting longer than one year is required before treatment.

Chronic Hepatitis C

- Serum ALT remains elevated 6 months after symptom onset; however, a normal ALT does not rule out the possibility of chronic hepatitis.
- Information on the genotype of the virus is an important guide for treatment decisions. Treatment is more effective for genotypes 2 and 3 than for genotypes 1 and 4.
- Patients with a positive HCV-RNA test, and permanently elevated ALT, most probably have mild chronic hepatitis, and treatment decisions can be made without liver biopsy in genotypes 2 and 3.
- Liver biopsy is indicated in patients with a suspicion of some other liver disease on top of HCV hepatitis.
- Treatment consists of a combination of interferon-alpha or pegylated interferon-alpha (Zeuzem et al., 2000; Heathcote et al., 2000; "Antiviral therapy for chronic hepatitis C", 2002; Shepherd et al., 2004) [**A**] and ribavirin (Brok, Gluud, & Gluud, 2005; Shepherd, Waugh, & Hewitson, 2000; "Chronic hepatitis C. Combination therapy IFN and ribavirin", 2002) [**A**] for 12 to 72 weeks in genotypes 1 and 4, and for 12 to 48 weeks in genotypes 2 and

3. The duration of treatment is determined by response. The effectiveness of treatment is monitored by HCV-PCR testing.
    - The treatment is discontinued if there is no response at 24 weeks at the latest (HCV-RNA still positive).
- With the combination therapy, the virus is eradicated from the blood in about 50% to 90% of the patients.
- Contraindications to the antiviral therapy are decompensated cirrhosis, severe liver dysfunction, cytopenia, immunosuppressive state, human immunodeficiency virus (HIV) positivity, drug or alcohol abuse, severe depression, autoimmune disease, severe generalized disease, and pregnancy.
- Due to the teratogenic effect of ribavirin, reliable birth control should be employed during the whole treatment and yet for 6 months after treatment. The same applies to partners of male patients receiving the treatment.
- Liver transplantation may be considered in advanced cirrhosis if there are no contraindications.

Ability to Work

- In the acute phase, sickness leave is allocated according to the normal principles (i.e., the patient may return to work as soon as his/her general condition allows).
- Chronic carrier state should not prevent the person from working.

Related Resources

Refer to the original guideline document for related evidence, including Cochrane reviews and other evidence summaries.

Definitions:

Classification of the Quality of Evidence

Code	Quality of Evidence	Definition
A	**High**	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial
B	**Moderate**	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	**Low**	Further research is very likely to have an important impact on

Code	Quality of Evidence	Definition
		confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	**Very Low**	Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence • One or more studies with very severe limitations

GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 (modified by the EBM Guidelines Editorial Team).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Concise summaries of scientific evidence attached to the individual guidelines are the unique feature of the Evidence-Based Medicine Guidelines. The evidence summaries allow the clinician to judge how well-founded the treatment recommendations are. The type of supporting evidence is identified and graded for select recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate evaluation and diagnosis, effective prophylaxis, and appropriate treatment of viral hepatitis

POTENTIAL HARMS

- Adverse effects of treatment
- Due to the teratogenic effect of ribavirin, reliable birth control should be employed during the whole treatment and yet for 6 months after treatment. The same applies to partners of male patients receiving the treatment.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to antiviral therapy are decompensated cirrhosis, severe liver dysfunction, cytopenia, immunosuppressive state, human immunodeficiency virus (HIV) positivity, drug or alcohol abuse, severe depression, autoimmune disease, severe generalized disease, and pregnancy.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Viral hepatitis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2008 Mar 10 [Various]. [2 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Dec 7 (revised 2008 Mar 10)

GUIDELINE DEVELOPER(S)

Finnish Medical Society Duodecim - Professional Association

SOURCE(S) OF FUNDING

Finnish Medical Society Duodecim

GUIDELINE COMMITTEE

Editorial Team of EBM Guidelines

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Maija Lappalainen; Martti Färkkilä

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Viral hepatitis. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2005 Oct 7 [Various].

GUIDELINE AVAILABILITY

This guideline is included in "EBM Guidelines. Evidence-Based Medicine" available from Duodecim Medical Publications, Ltd, PO Box 713, 00101 Helsinki, Finland; e-mail: info@ebm-guidelines.com; Web site: www.ebm-guidelines.com.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 2, 2005. This NGC summary was updated by ECRI on November 8, 2005. This NGC summary was updated by ECRI Institute on December 23, 2008.

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